Perspective

Why is the mammary artery so special and what protects it from atherosclerosis?

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The internal mammary artery (IMA) grafts have been associated with long-term patency and improved survival as compared to saphenous vein grafts (SVGs). Early failure of IMA is attributed to poor surgical technique and less with thrombosis. Similarly, bypass surgery especially with the use of IMA has also been shown to be superior at 1-year as well as over five years compared to percutaneous procedures, including the use of drug-eluting stents for the treatment of coronary artery disease. The superiority of IMAs over SVGs can be attributed to its striking resistance to the development of atherosclerosis. Structurally its endothelial layer shows fewer fenestrations, lower intercellular junction permeability, greater anti-thrombotic molecules such as heparin sulfate and tissue plasminogen activator, and higher endothelial nitric oxide production, which are some of the unique ways that make the IMA impervious to the transfer of lipoproteins, which are responsible for the development of atherosclerosis. A better comprehension of the molecular resistance to the generation of adhesion molecules that are involved in the transfer of inflammatory cells into the arterial wall that also induce smooth muscle cell proliferation is needed. This basic understanding is crucial to championing the use of IMA as the first line of defense for the treatment of coronary artery disease.

Keywords: Coronary artery disease; internal mammary artery (IMA); pathology; saphenous vein graft (SVG)

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Introduction

The internal mammary arteries (IMAs) are commonly used as the conduit to bypass major coronary artery stenosis, and have shown greater long-term patency rates and improved survival as compared to saphenous vein grafts (SVGs) (1,2). The benefit of IMAs over SVGs on mortality has been consistently observed irrespective of age, gender, degree of luminal stenosis in the left main coronary artery or preoperative left ventricular function with the survival differences widening over time (3). The main differences are related to the development of atherosclerosis which has rarely been observed in the IMA graft while it develops at a fairly rapid rate in the SVG (4,5)

Since the publication by Loop *et al*. in 1986 on 10-year survival of patients who received an IMA graft to the left anterior descending coronary artery (LAD) with or without one or more vein grafts versus patients who received only SVGs, which showed that the survival was higher with an IMA graft (93.4%) versus SVG (88.0%) for those with one-vessel disease, 90.0% versus 79.5% for two-vessel disease, and 82.6% versus 71.0% (P<0.0001) for those with three-vessel disease, the IMA has become the preferred choice for grafting the LAD (6). SVGs are known to undergo not only intimal thickening but also atherosclerosis, and angiographic studies demonstrated a 2% per year vein-graft attrition rate from the 1st to the 7th postoperative year, further increasing to 5% per year from the 7th to the 12th year (5). At 10-years, it has been reported that only 38% to 45% of SVG remain patent (6,7). These studies have helped document the superiority of IMA graft over SVG.

Comparative anatomy of IMA and SVG

The IMA is an elastic artery which arises from the

subclavian artery. In adults the diameter of the IMA varies from 1.9 to 2.6 mm, with a wall thickness of 180 to 430 microns (8). The intima consists of endothelium with some neointima, which is seen in up to 50% of cases and rarely (13%) is there a substantial neointima which is greater than the medial thickness (8). The media consists of discreet lamellae of collagen and smooth muscle cells (SMCs) that are located between the elastic layers and are aligned circumferentially. The number of elastic layers varies from 7 to 11, depending upon the thickness of the wall of the IMA. The adventitia has been shown to possess very few vasa vasorum (9,10). On the other hand, the SVG has a larger diameter (3.1 to 8.5 mm) and its wall thickness ranges from 180 to 650 microns. The vein has longitudinally oriented bundles of SMCs in the inner media and adventitia and the circumferentially oriented medial cells are in between the longitudinal fibers. Type I collagen separates the longitudinally oriented SMC bundles and is also interspersed between the circumferentially oriented SMCs. Elastic lamellae are observed in the intima, media and adventitia; in the latter, the fibers are interspersed between collagen fibers. In the intima, there is no prominent internal elastic lamina; however, multilayered appearance is observed with interspersed SMC and collagen. Intimal thickening has been described to be almost always seen in vein grafts at the time of implantation; however, in 90% of cases it occupies <25% of the cross sectional area (8,11).

Histologic changes observed in long-term IMA graft versus SVG

It is well known that SVGs are susceptible to accelerated atherosclerosis as compared to native coronary arteries or IMAs, thus limiting the long term benefits of coronary artery bypass graft (CABG) surgery with SVGs. SVGs at the time of implantation show focal absence of endothelium with platelet and fibrin deposition along the intimal surface. Acute inflammatory cells are often observed in the wall of the graft. Vein grafts in place for more than one month show diffuse intimal thickening consisting of SMCs, proteoglycans and collagen. The mechanisms responsible for rapid neointimal growth in SVGs are believed to involve response to endothelial injury along with hemodynamic stress as the vein wall is now subjected to arterial pressures. SVGs implanted for over one year show arterialization and fibrointimal thickening that consists of SMCs, proteoglycans, and type I and III collagen. The degree of intimal thickening varies and is reported to be usually <75% cross-sectional area narrowing with <10% demonstrating >75% narrowing from neointimal tissue only (11). Patients with fibrointimal proliferation have been shown to have higher systolic and diastolic blood pressure (12). Atherosclerotic change in vein grafts has been observed as early as 13 months. The earliest change consists of foam cell accumulation overlying neointimal thickening, which is observed close to the luminal surface and is usually extensive. Foam cell accumulation is soon followed by the presence of a necrotic core, which is observed between 1 to 3 years. SVGs implanted for more than five years frequently exhibit a large necrotic core, with hemorrhage that likely occurs both from the lumen and less often from adventitial neoangiogenesis extending into the intima, leading to expansion of the necrotic core and eventually plaque rupture (4).

The changes of atherosclerosis in SVGs also correlate with the presence of risk factors as they do for native coronary arteries. We have shown a good correlation of total cholesterol with the development of vein graft atherosclerosis. Aggressive treatment with lovastatin achieving LDL-cholesterol (LDL-C) <100 mg/dL resulted in only 27% of grafts with progression of atherosclerosis while moderate treatment resulted in 39% of grafts with progression (13), and low dose warfarin therapy had no effect on atherosclerosis. Although much progress has been made in the understanding of SVG disease to increase survival, the best results, even with aggressive lipid lowering do not parallel those with the use of IMA grafts (14).

Early IMA graft failure is most commonly attributed to technical errors with harvesting and the graft anastomosis. IMA grafts examined within the first week following distal anastomosis show an absence of neointimal thickening or there are only a few SMC along with proteoglycan and collagen. When IMA grafts are examined between 1 week and 2 months, the site of the anastomosis shows intimal thickening (0.08±0.07 mm) located at the cleft between the native artery and the IMA graft at the anastomotic suture site (*Figure 1*) (15). The intimal thickening consisted of SMCs, proteoglycan, collagen and elastin fibers with luminal endothelial cells. However, in the body of the graft at this time, there are only occasional areas that show minimal intimal thickening consisting of a few SMCs in a proteoglycan matrix with or without collagen, likely due to manipulation of the artery at the time of surgery. Significant intimal thickening was observed in grafts implanted for 2 months to 10 years at the suture sites

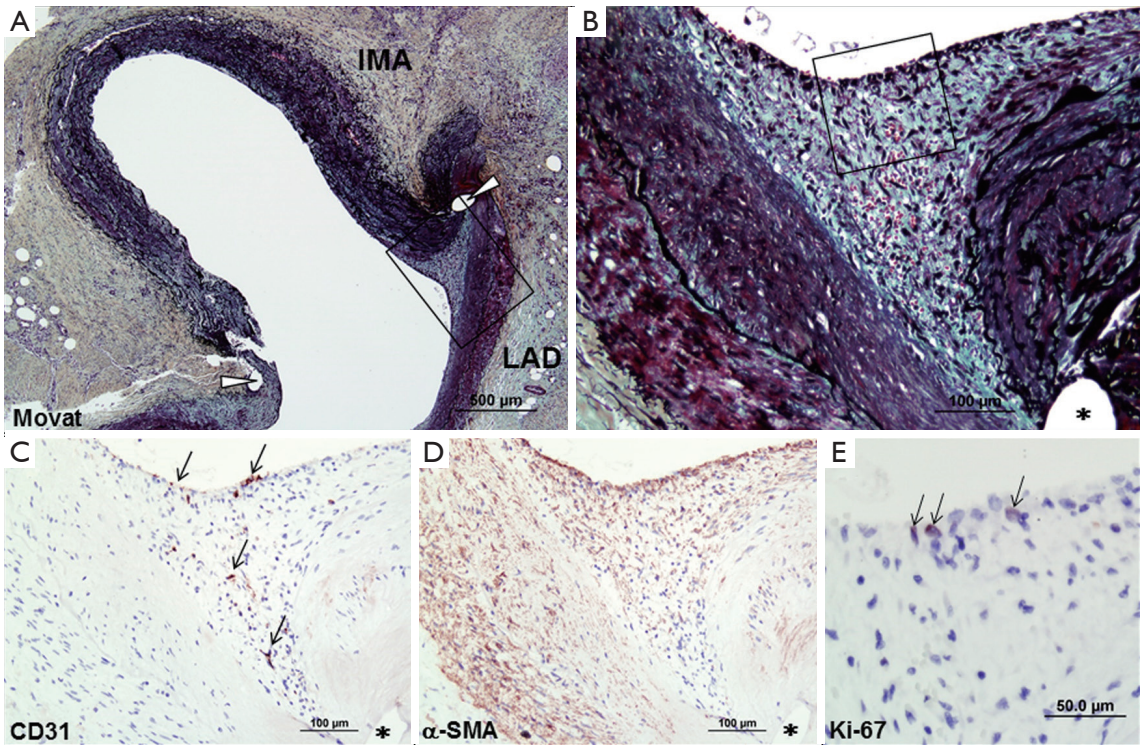

Figure 1 Early histologic changes in the internal mammary artery (IMA) graft obtained from a 69-year-old man who underwent coronary artery bypass graft (CABG) surgery 1 week antemortem. A and B. A low (A) and a high (B) power images (Movat pentachrome) showing the site of IMA anastomosis (arrow heads in A and * in B indicate suture sites) with the left anterior descending artery (LAD). Note the presence of intimal thickening in the cleft between the native artery and the IMA graft at the anastomotic suture site, which consists of smooth muscle cells (SMCs) in a proteoglycan (blue/green) matrix with angiogenesis, few red blood cells and luminal endothelial cells; C. The presence of luminal endothelial cells and areas of angiogenesis (arrows) within the neointima are highlighted by immunostaining by anti-CD31; D. Shows that the majority of the neointimal cells consists of α-smooth muscle actin (α-SMA) positive cells; E. Immunostaining for a nuclear protein Ki-67 confirms the presence of rare proliferative cells (arrows) within the neointima close to the luminal surface (the area corresponds with the black box in B)

(0.39±0.17 mm) and on the hood (0.29±0.25 mm), while intimal thickening on the floor (native LAD) was observed in 10 of 18 IMA grafts (0.11±0.12 mm) (*Figure 2*). Intimal thickening is similar in those grafts less than 1 year versus grafts greater than 1 year, suggesting that intimal thickness does not increase with time. The body of the IMA graft also showed the least intimal thickening as compared to the anastomotic site (10 of 18, 0.03±0.04 mm). Only rarely was an atherosclerotic change observed in the IMA. In our study, 2 of the 18 grafts examined 5.22±4.76 years following grafting, it was described as "small focal, infiltrates of lipid in the intima".

Our published long-term morphologic data in IMA grafts versus SVGs was reported in 1988 (5), where 18 IMAs were compared to 15 SVGs from 18 patients with duration of grafts between 12 to 118 months (mean, 56 months) that had been removed either surgically or at necropsy. We found that fibrointimal proliferation alone was more frequent in IMAs as compared to SVGs [IMA; 8 of 18 (44%) versus SVG; 4 or 15 (27%)]. However, since vein grafts beyond one year are often accompanied by foam cell infiltration, with or without a necrotic core, such changes were observed in 9 of 15 SVGs (60%). In contrast, atherosclerosis was extremely rare in IMA grafts and was only observed in 1 of 18 IMA (6%) (*vs.* SVG, P=0.01) and that too consisted of only a few foam cells within the neointimal tissue in a graft which showed severe stenosis at the anastomotic site at 3 years.

Not only has the left IMA graft to the LAD been demonstrated to remain patent and improve longevity

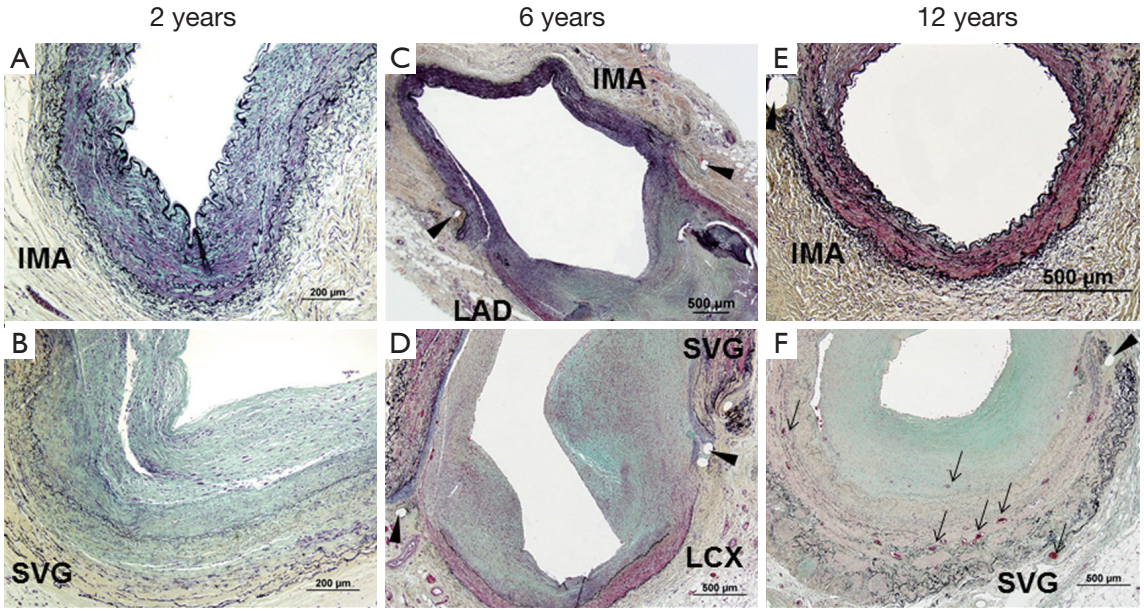

Figure 2 Histologic changes observed in the internal mammary artery (IMA) graft as compared to the saphenous vein graft (SVG). A,B. Histologic sections showing IMA and SVG obtained from a 76-year-old man who underwent coronary artery bypass graft (CABG) surgery 2 years antemortem. IMA shows no or rare intimal smooth muscle cells (SMCs) whereas SVG exhibit moderate neointimal growth with few SMCs but rich in matrix which consists of proteoglycans and collagen; C,D. Histologic sections showing IMA and SVG obtained from a 69-year-old man who underwent CABG surgery 6 years antemortem. Note the absence of intimal thickening in IMA (C) versus the presence of moderate neointimal thickening in SVG from SMCs and proteoglycan-collagenous matrix at the site of anastomosis (arrow heads indicate suture sites) with left anterior descending artery (LAD) or left circumflex artery (LCX) (D); E,F. IMA graft and SVG from a 77-year-old woman who underwent CABG surgery 12 years antemortem. While the IMA shows minimal intimal thickening, SVG exhibits moderate to severe neointimal growth with proteoglycan-collagen matrix and angiogenesis (arrows). All sections were stained with Movat pentachrome

at 10- and 15-years, bilateral IMA has an additional effect of reducing myocardial infarction, reoperation and percutaneous coronary interventions (PCI) (16). Similarly, skeletonization of the IMA had no effect on long-term patency, but added extra length. However, this also carries the possibility of decreased risk of deep sternal infection, which is likely related to significant postoperative reduction in sternal perfusion (17). Bilateral IMA are also increasingly being used as Y- or T-composite arterial grafts for treating 3-vessel coronary artery disease. The short-term blood flow reserve results have been good (18), with long-term data required to confirm patency.

What protects IMA from atherosclerosis?

The superiority of IMAs over SVGs with less mortality and greater patency rates (>90% at 10 years) could be attributed to the striking resistance of this conduit to atheroma, where multiple structural and physical properties of the IMA could be involved (*Table 1*) (19). It is interesting to note that IMA grafting of the LAD is also associated with less progression of native atherosclerotic disease within the proximal LAD as compared to when a vein graft is anastomosed to the LAD, as well as greater and rapid native disease progression from the development of fibrosis and calcification.

Role of endothelial cells in IMA patency

The IMA endothelium shows fewer fenestrations and lower intercellular junction permeability as compared to SVG, which could prevent lipoproteins from entering the subendothelial space. Segments of IMA collected at the time of surgery show a preserved morphology without any disturbance of endothelial cells or cautery burns, with uniform platelet endothelial cell adhesion molecule-1 (PECAM-1) staining, and strong expression of glucose transporter 1. Conversely, inducible nitric oxide synthase

Table 1 Comparative anatomic and physiological properties of internal mammary artery (IMA) and saphenous vein (reproduced with permission from Motwani JG and Topol EJ. Circulation 1998;97:916-31.)

	IMA	Saphenous vein
Anatomic properties		
Endothelial fenestrations	Few	Many
Intercellular (IC) processes	Many	Few
IC junction permeability	Low	High
Internal elastic lamina (IEL)	Well defined	Poorly defined
Heparan sulfate in IEL/media	High	Low
Dependence on vasa vasorum	Minimal	High
Valves	Absent	Present
Size match with grafted native vessel	Good	Poor
Resistance to trauma of harvesting	High	Low
Physiological properties		
Flow reserve	High	Low
Shear stress	High	Low
Nitric oxide/prostacyclin production	High	Low
Vasomotor response to thrombin	Relaxation	Constriction
Vasoconstrictor sensitivity	Low	High
Vasodilator sensitivity	High	Low
Basic fibroblast growth factor receptors	Few	Many (8× IMA)
Lipolysis	Rapid	Slow
Lipid synthesis	Less active	More active
Lipid uptake	Slow	Rapid

(iNOS) and intercellular adhesion molecule-1 (ICAM-1) are only moderately expressed on the luminal surface as well as on vasa vasorum of IMAs removed from patients with acute coronary syndrome or chronic stable angina (20). Endothelial cells of the IMA are rich in heparin sulfate and endothelial nitric oxide synthase (eNOS), and release a greater amount of nitric oxide (NO) that contributes to the antithrombotic properties and endothelial homeostasis which confers protection from atherosclerosis.

It has been reported that female sex is a well-defined independent predictor of poor outcome following bypass grafting. The differences between men and women have been attributed to technical and anatomic factors, especially smaller body size with smaller coronary artery size. It has been shown that age-related impairment of NO production is likely enhanced in post-menopausal women and is ascribed to the loss of the protective effects of estrogens. Recently, Mannacio *et al*. (21) have shown that IMA endothelial cells from menopausal women have impaired expression of messenger RNA for eNOS and reduced eNOS protein levels as compared to age matched men and younger women.

Blood flow and the endothelium

Blood flow creates two principal vectors on the vessel wall, one which is perpendicular to the wall and is determined by the blood pressure, and the other which is parallel to the vessel wall and creates frictional force and shear stress on the endothelial cells. Endothelial cells align in the direction of flow but the orientation is lost with flow disturbances. The stress on the surface of the endothelial cells leads to cytoskeleton changes that attach the endothelial cell to the subendothelial matrix and to adjacent cells, leading to increased resistance to deformation and impart stability. Endothelial cells sense shear-stress and are the principal endothelial regulator of arterial diameter, which may be related to the release of NO. Other substances that also mediate vaso-regulation include prostaglandin I2, endothelin-1, tissue plasminogen activator, ICAM-1,

and transforming growth factor-β1 (TGF-β1). While the effects of NO are short-lived, NO synthesis is enhanced by the steady laminar flow that induced eNOS. The arterial remodeling seen in the IMA occurs over months and is a response to flow that result in changes in gene expression. Chronic flow increase results in enlargement of the arterial lumen whereas reduced flow induces intimal thickening and a reduction in vessel lumen. This has been demonstrated in the canine IMA following reduction of flow by ligation of the side branch (22). The IMA has an abundant collateral blood supply to its runoff bed, which also lead to the protection of the intima (23). Furthermore, the size of the IMA is close to the size of the coronary vessels, which may result in less turbulent flow as compared to the larger SVG conduits that are prone to develop atherosclerosis.

SVG must undergo adaptive changes ("arterialization") when placed in the high pressure aorta-coronary circulation, whereas the IMA is already accustomed to the high left-sided circulation pressures. Flow reserve in the IMA is higher than that in SVGs, and the IMA graft may have the ability to enlarge substantially over years (24). Porto *et al*. (25) have recently reported the results of quantitative coronary angiography (QCA) and frequency-domain optical coherence tomography (FD-OCT) to determine long-term morphofunctional remodeling of left IMA (LIMA) grafts versus *in situ* right IMA (RIMA) in the same patients with the duration of the LIMA grafts more than 10 years. Baseline mean diameter and area of LIMA grafts were significantly smaller than that of *in situ* RIMA. FD-OCT revealed that the LIMA as compared to the RIMA had a larger mean intimal area [LIMA =0.50 mm^2 (0.37-1.02 mm^2) versus RIMA =0.30 mm^2 (0.20-0.45 mm^2); P=0.05] and greater maximal intimal thickness [LIMA =156.5 μm (77.7-186.2 μm) versus RIMA =45.0 μm (29.0-70.3 μm); P=0.01] with a non-significant medial thinning. Intimal-media ratio was greater in LIMA as compared to RIMA [LIMA = 0.72 (0.53-0.91) versus RIMA =0.23 (0.12-0.38); P=0.02]. Furthermore, endothelium-dependent and independent vasodilation was tested by selective infusion of acetylcholine (ACh) and isosorbide dinitrate (ISDN), where vasodilatory response as determined by percentage increase of mean lumen diameter did not differ between the LIMA and the RIMA. Despite the intimal thickening present in the LIMA, both the LIMA and the RIMA have a similar response to vasodilators. Although a mismatch between vasodilatory response and intimal thickening was only observed in LIMA, this might represent an adaptive response to different flow pattern encountered in LIMA versus RIMA following CABG.

Coronary artery bypass grafting (CABG) as compared to percutaneous coronary intervention (PCI)

CABG has been the treatment of choice compared to balloon angioplasty since results from the Bypass Angioplasty Revascularization Investigation (BARI) trial in 1996, of patients with multi-vessel coronary disease, showed patients with CABG lived longer than patient undergoing balloon angioplasty (26). Since the advent of drug-eluting stents (DES), interventional cardiologists have contended that CABG may not be superior to stenting because of improved results with DES over bare metal stents or balloon angioplasty. With the use of 1st-generation DES in the SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study, it was shown that all cause death or myocardial infarction was not different in the two arms; however, repeat vascularization was significantly more frequent in PCI than CABG (13.5% *vs*. 5.9%, P<0.001) in the first year. The differences in myocardial infarction and repeat PCI have now been both shown to be significantly lower for CABG as compared to PCI at 3- and 5-years. These results are also similar to those in the recently published ASCERT study (27), which was a large non-randomized observational data from The Society of Thoracic Surgeons and the American College of Cardiology Foundation registries to evaluate effectiveness of revascularization with CABG compared to PCI. This too showed a benefit for CABG with a 4-year mortality of 16.4% in the CABG arm versus 20.8% in the PCI arm (risk ratio, 0.79; 95% confidence interval 0.76-0.82) (27). Similar results have also been published for the FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trial. The primary outcome of composite of death from any cause, non-fatal myocardial infarction, or nonfatal stroke occurred more frequently in the PCI than in the CABG group (P=0.005), with 5-year rates of 26.6% in the PCI and 18.7% in the CABG group (28). Both the SYNTAX and the FREEDOM trials had over 94% of patients undergoing left IMA to LAD grafting, thus showing that even with much improvement in the DES, patients with multi-vessel disease should undergo CABG preferably with as many arterial grafts as possible (however this was not demonstrated in the trials). Although many patients do not want a sternotomy, it is possible to

advocate a minimally invasive direct coronary artery bypass surgery (MIDCAB), which has shown promising results in expert surgical hands (29). It is also possible to carry out hybrid procedures with IMA to LAD and DES in right or the circumflex coronary arteries, as indicated. This will require better cooperation between the surgeons as well as the interventionist, although this has not been true in the past. However, with the advent of transcatheter aortic valve replacement (TAVR), there appears to be greater cooperation and more of an atmosphere of congeniality. If we take the oath as physician "The health of my patient will be my first consideration" to heart then everyone will win; the surgeon, the interventionalist, the cardiologist, and the patient (30).

Conclusions

There is little doubt that the IMA is a superior graft than the saphenous vein, so it behooves all thoracic surgeons to take the time and care to carry out CABG with an IMA and to use as many arterial grafts as possible. We may not have all of the information as to why the IMA graft is far superior to vein grafts, but this understanding is increasing. A better comprehension of the uniqueness of the IMA's mechanical factors, such as shear stress forces, endothelial cell attachment with tight endothelial junctions and biochemical generation of important molecules like nitric oxide and anti-thrombotic factors, and resistance to the generation of selectins and other adhesion molecules, may help to understand why the IMA is resistant to the development of atherosclerosis. Similarly, we need to understand why the SMC of the IMA are resistant to proliferation and remain phenotypically contractile for decades. With increased understanding, it is more likely that we will be able to transfer such knowledge to the prevention of atherosclerosis in native arteries too.

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